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1632

PTO/SB/21 (02-04)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/903,376
Filing Date	July 10, 2001
First Named Inventor	Thomas J. Brennan
Art Unit	1632
Examiner Name	Peter J. Paras, Jr.
Attorney Docket Number	R-599

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- ☑ Fee Transmittal Form
- ☐ Fee Attached
- ☑ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☑ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☑ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance communication to Technology Center (TC)
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Kelly L. Quast, Reg. No. 52,141
Signature	Kelly L Quast
Date	02-20-2004

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Don Mixon		
Signature	Don Mixon	Date	02-20-2004

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/17 (10-03)
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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($)

Complete if Known	
Application Number	09/903,376
Filing Date	July 10, 2001
First Named Inventor	Thomas J. Brennan
Examiner Name	Peter Paras Jr.
Art Unit	1632
Attorney Docket No.	R-599

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-1271

Deposit Account Name: Deltagen, Inc.

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☐ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	475.00
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 475.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	Kelly L. Quast	*Registration No. (Attorney/Agent)*	52,141	*Telephone*	650-569-5100
Signature	Kelly L Quast			*Date*	02-20-2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

	Application No.	Applicant(s)	
Office Action Summary	09/903,376	BRENNAN, THOMAS J.	
	Examiner	**Art Unit**	
	Peter Paras, Jr.	1632	

The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-7,9,11-16 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending.

Election/Restrictions

Applicant's election without traverse of Group III, claims 8, 10, and 17-23) in Paper No. 13 is acknowledged.

Claims 1-7, 9, 11-16, and 24-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached **N**otice To Comply With Requirements For Patent Applications Containing **N**ucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. *Any* response to this Office Action, which fails to meet all of these requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

To avoid damage to a CRF by irradiation, a reply to a notice to comply with the sequence rules should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:
1. Electronically submitted through EFS-Bio (**<http://www.uspto.gov/ebc/efs/downloads/documents.htm>**, EFS Submission User Manual - ePAVE)
2. Mailed to: **U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202**
3. Mailed by Federal Express, United Parcel Service or other delivery service to: **U. S. Patent and Trademark Office, 2011 South Clark Place, Customer Window, Box Sequence, Crystal Plaza Two, Lobby, Room 1B03, Arlington, Virginia 22202**
4. Hand Carried directly to the Customer Window at: **2011 South Clark Place, Crystal Plaza Two, Lobby, Room 1B03, Box Sequence, Arlington, Virginia 22202**

Drawings

The drawings filed on 7/10/01 are approved.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 10, and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to making and using a transgenic non-human animal, particularly a mouse, comprising a disruption in the 5-HT-2B gene.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1, wherein SEQ ID NO: 1 encodes a 5-HT-2B. See pages 3-4 and the working example on pages 51-53, of the specification. The specification teaches that transgenic mice whose genomes comprise a homozygous disruption in a 5-HT-2B gene exhibit lethality between embryonic days 8.5 and 9.5, as a result of the disruption. See pages 51-53 of the specification. While discussing that embryos comprising a homozygous disruption of a 5-HT-3B gene die before birth the specification has not disclosed a particular phenotype exhibited by the embryos. The specification has also not disclosed a phenotype exhibited by a transgenic non-human animal comprising a heterozygous disruption of a 5-HT-2B gene. As the specification has not provided guidance that correlates to a phenotype resulting from disruption of a 5-HT-2B gene in a transgenic non-human animal, the specification has not taught how to use the transgenic non-human animals embraced by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support how to use such a mouse. See pages 51-53. Given the lack of guidance provided by the instant specification it would have required undue experimentation to use the transgenic non-human animals embraced by the claims.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 8, 10 and 17-23 as they read on transgenic knockout non-human animals, use of embryonic stem cells to make a transgenic mouse, and germline transmission of ES cells:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a 5-HT-2B gene other than a transgenic knockout mouse. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). Moreover, with regard to claims 10 and 22 neither the state of the art nor the prior art of record has provided guidance for use of cells, other than ES cells for production of a transgenic knockout mouse. It would be unpredictable if other cells could be used for the

production of a transgenic knockout mouse because other cells may be not totipotent or transmit through the germline as ES cells do. Even more, claims 8, 10 and 17-23 as written do not appear to require germline transmission of the disrupted nucleotide sequence. These claims may be broadly interpreted to read on a single cell comprising a disrupted nucleotide sequence. Since the claims do not require germline transmission of the disrupted nucleotide sequence it would be unpredictable if an ES cell comprises the disrupted nucleotide sequence. As stated above the evidence of record does not support germline transmission of non-ES cells. As the claims are directed to transgenic non-human animals (claim 8) or a method that requires the use of a cell to in the production of a transgenic mouse (claims 10 and 22), wherein the cell is interpreted to read on an embryonic stem cell (as in claims 10 and 22) comprising a disruption in a 5-HT-2B gene, which must be generated by the introduction of a transgene into an ES cell or transgenic non-human animals, particularly a mouse, that do not exhibit germline transmission of a disrupted nucleotide sequence, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

As a final issue the claims encompass transgenic non-human animals, particularly a mouse, that comprise a disruption in a 5-HT-2B gene that do not exhibit any particular phenotype specific resulting specifically from the disruption. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see

page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a 5-HT-2B. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. The specification discloses that homozygous knockout mice comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1 do not exist as the homozygous embryos die between days 8.5 and 9.5 during development and never develop to term. See pages 51-53 of the specification. The specification suggests that the homozygous knockout embryos exhibit embryonic lethality, abnormalities, retarded development, and are reabsorbed. Claim 17 however is directed to a transgenic mouse that exhibits embryonic lethality, abnormal embryos, retarded development, and reabsorbed embryos. It appears that the claims embrace a transgenic mouse that cannot exist as only the homozygous embryos die and are abnormal. Furthermore, such alleged phenotypes are overly broad and appear to be general, as abnormalities and retarded development appear to relate to any embryo that dies during development. In addition, the instant specification has not provided guidance that correlates to a phenotype resulting from a heterozygous disruption of a 5-HT-2B gene. As such it appears that a transgenic mouse comprising a heterozygous disruption of a 5-HT-2B gene does not exhibit a phenotype that differs from a wild-type mouse. Moreover, the skilled artisan would not know how to use a

transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice that have a phenotype may be used for drug testing or as models for diseases or disorders according to the instant specification. It is noted that claim 8 does not recite a phenotype resulting from disruption of a 5-HT-2B gene. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a 5-HT-2B gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a 5-HT-2B gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a phenotype, the unpredictable state of the art with respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to any phenotype associated with embryonic lethality, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER

Application No.:09/903,376

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

[X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

[ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

[ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

[ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

[ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

[ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

[X] 7. Other: Fig. 2A contains an unidentified sequence.

Applicant Must Provide:

[X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

[X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

[X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support (SIRA)
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

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Underlined = deleted in targeting construct

Bold = sequence flanking Neo insert in targeting construct

ACTGTCTGGAACTGGACTGAGTCACCAAAAGGCGAATGGCTTCATCTTATAAAATGTCTG
AACAAAGCACAACTTCTGAGCACATTTTACAGAAGACATGTGATCACCTGATCCTGACTA
ACCGTTCTGGATTAGAGACAGACTCAGTAGCAGAGGAAATGAAGCAGACTGTGGAGGGAC
AGGGGCATACAGTGCACTGGGCAGCTCTCCTGATACTCGCGGTGATAATACCCACCATTG
GTGGGAACATCCTTGTGATTCTGGCTGTTGCACTGGAGAAAAGGCTGCAGTACGCTACCA
ACTACTTTTTAATGTCCTT **GGCGATAGCAGATTTGCTGGTTGGATTGTTTGTGATGCCGA**
TTGCCCTCTTGACAATCATGTTTGAGGCTATATGGCCCCTCCCACTGGCCCTGTGTCCTG
CCTGGTTATTCCTCGATGTTCTCTTTTCAACTGCCTCCATCATGCATCTCTGTGCCATTT
CCCTGGACCGCTATATAGCCATCAAAAAGCCAATTCAGGCCAATCAGTGCAACACCCGGG
CTACTGCATTCATCAAGATTACAGTGGTATGGTTAATTTCAATAGGCATCGCCATCCCAG
TCCCTATTAAAGGAATCGAGACTGATGTGATTAATCCACACAATGTCACCTGTGAGCTGA
CAAAGGACCGCTTTGGCAGTTTTATGGTCTTTGGGTCACTGGCTGCTTTCTTCGTACCTC
TCACCATCATGGTAGTCACTTACTTTCTCACCATTCACACTTTACAGAAGAAAGCTTACT
TGGTCAAAAATAAGCCACCTCAACGCCTAACACGGTGGACTGTGCCCACAGTTTTCCTAA
GGGAAGACTCATCCTTTTCATCACCAGAAAAGGTGGCAATGCTGGATGGGTCTCACAGGG
ATAAAATTCTACCTAACTCAAGTGATGAGACACTTATGCGAAGAATGTCCTCAGTTGGAA
AAAGATCAGCCCAAACCATTTCTAATGAGCAGAGAGCCTCGAAGGCCCTTGGAGTCGTGT
TTTTCCTTTTTCTGCTTATGTGGTGCCCCTTTTTTATTACAAATCTAACTTTAGCTCTGT
GTGATTCCTGCAATCAGACCACTCTCAAAACACTCCTGGAGATATTTGTGTGGATAGGCT
ACGTTTCCTCGGGGGTGAATCCTCTGATCTATACACTCTTCAATAAGACATTTCGGGAAG
CATTTGGCAGGTACATCACCTGCAATTACCGAGCCACAAAGTCAGTAAAAGCACTTAGGA
AGTTTTCCAGTACACTTTGTTTTGGGAATTCAATGGTAGAAAACTCTAAATTTTTCACAA
AACATGGAATTCGAAATGGGATCAACCCTGCCATGTACCAGAGCCCAATGAGGCTCCGAT
GTTCAACCATTCAGTCCTCATCAATCATCCTCCTCGATACCCTTCTCACTGAAAACGATG
GCGACAAAGCGGAAGAGCAGGTCAGCTACATATTGCAGGAACGGGCCGGCCTCATCTTGA
GAGAGGGTGATGAGCAGGACGCACGCGCACCATGGCAGGTTCAAGAGTGA
(SEQ ID NO:1)

FIGURE 2A

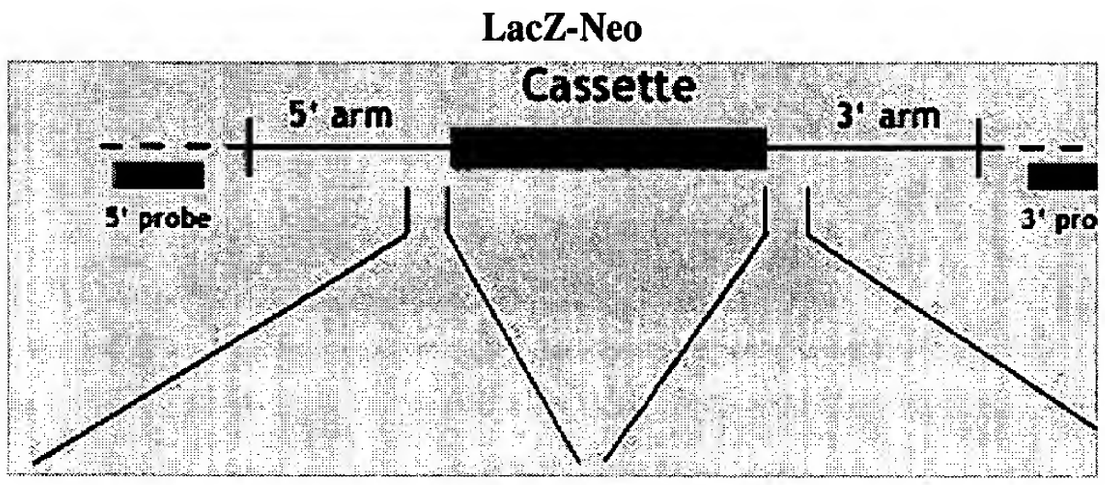
Gene Sequence Structure *

130 bp Sequence Deleted 319 bp

Size of full-length cDNA: 1550 bp

Targeting Vector* (genomic sequence)

Construct Number: 2520



Arm Length:
5': 1.6 kb
3': 5 kb

Targeting Vector
Endogenous Locus

* Not drawn to scale

5'>TGAGTGTCTGGTGGGTTTG CT AAATGCTTTGCTAAAGCAGATG AC TTGCTTAGCTACTGACCATGCT GA CCACTGTCTGGAACTGGACTGA GT CACCAAAAGGCGAATGGCTTCA TC TTATAAAATGTCTGAACAAAGC AC AACTTCTGAGCACATTTTACAG AA GACATGTGATCACCTGATCCTG AC TAACCGTTCTG<3' (SEQ ID NO:3)	5'>GGCGATAGCAGATTTGCTG GT TGGATTGTTTGTGATGCCGATT GC CCTCTTGACAATCATGTTTGGT GA GTATTTCCCCTTGTTCCTGCCA CT GAACACTACTAACGTAGTGAAA TG GACACTCACTGACCTTTATTTT GT TTGAAATAAAAGAAGGACCTGG AT TAAAAACACAGAAGGGAACATT CC TTCATTTTTCA<3' (SEQ ID NO:4)

FIGURE 2B